REMARKS

Claims 50 to 72 are pending. Support for the new claims derive from the specification and claims as originally filed. Accordingly, the claims do not present new matter and entry is proper. Applicant reserves the right to claim additional subject matter and additional substitution positions in later cases.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 28-49 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

6a. Claim 28 is rejected as vague and indefinite because it is unclear as to what receptor if any signaling activation is affected by mixed trimers of TNF. Applicant believes the new claims render the rejection moot

6b. Claims 29-45 are rejected as vague and indefinite because the claims call for one or more amino acid substitutions compared to naturally occurring human TNF. The rejection is believed moot in light of the claim amendments. Applicant notes that the Examiner agrees that the claimed substitutions may be done either individually or in combination and that this meets the written description and enablement provisions of 35 U.S.C. §112, first paragraph. Thus, Applicant asserts that multiple substitutions, as claimed, are fully enabled.

6c. Claims 29-49 are rejected as vague and indefinite because the claims call for at least one amino acid substitution but do not require any conservation of structure or function. Applicant believes the new claims render the rejection moot.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 37, 46-48 are rejected under 35 USC § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

7a. The Examiner states at page 4, starting at line 1 that the Examiner cannot find support for certain amino acid substitutions. Substitution A84V may be found in Table 7 as Clone 73. As for the remaining variants listed, they appear in Table 11.

7b. Claim 28 is rejected under 35 USC § 112, first paragraph, for lack of written description.

Applicants respectfully submit that the specification provides written description support and enables a genus of variant TNF-α proteins as disclosed in the present claims.

As stated above, Applicants have added a reference sequence against which to compare the variants. The variants of the present invention are designed to interact with naturally occurring TNF-α, including allelic variants, in order to sequester the naturally occurring TNF-α and inhibit or decrease activation of TNF-α receptor signaling. The variants of the present invention do not include naturally occurring TNF-α (including allelic variants) within its scope.

Only certain variants meet the recited criteria of the claims, and certainly not all variant TNF-α sequences with one or more amino acid substitutions. Further, there is no maximum number of changes to the human TNF-α and yet retain the TNF-α activity, as stated by the Examiner at page 5 of the Office Action, as the claims include a functional limitation.

Applicants respectfully point to In re Goffe, 191 USPQ429 (CCPA 1976), where the court stated:

> "For all practical purposes, the Board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found to work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional propose of promoting progress in the useful arts."

Additionally, in In re Angstadt, 190 USPQ 214, 218 (CCPA 1976), the court further stated:

> "Appellants have apparently not disclosed every catalyst which will work; they have apparently not disclosed every catalyst which will not work. The question, then, is whether in an unpredictable art, section 112 requires disclosure of a test with every species covered by a claim. To require such a complete disclosure would apparently necessitate a patent application or applications with "thousands" of examples or the disclosure of "thousands" of catalysts along with information as to whether each exhibits catalytic behavior resulting in the production of hydroperoxides. More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed."

These cases show that the invention should not be limited to examples or preferred embodiments, but to the real scope of the invention. Claim 28 describes the scope of the invention and is supported by the written description in the specification.

7c. Claims 29-45 are rejected under 35 USC § 112, first paragraph, for lack of written description. Applicant believes the new claims render this rejection moot.

7d. Claims 29-37 and 40-49 are rejected as not being fully enabled. Applicant believes the new claims render this rejection moot, as the claims reflect the material that the Examiner has found to be enabling.

However, Applicant maintains the enablement of the original claims. The Examiner cites *In re Wands*, 858 F.2d 731, 73, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) and states that it would require undue experimentation to practice the claimed invention. Whether or not undue experimentation is required to make and use an invention is to be determined based on several factors, including those enumerated in *In re Wands*, (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of skill of the ordinary artisan; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the

existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims do not go beyond what is disclosed in the examples, tables and Figures of the specification; based on the extent of the disclosure and the general level of knowledge and skill in the art, practicing this invention is well within the reach of the ordinary skilled artisan. The invention is in a field that is established enough to have some basic concepts, such expression and generation of protein variants, assaying the protein variants, etc., confidently established. Furthermore, the artisan in the field of protein engineering is highly skilled. The specification provides ample direction, and the knowledge in the field is very extensive regarding general techniques. The specification provides working examples and details the specific variants generated. Furthermore, while some experimentation would be necessary, it would not be considered other than routine, given the disclosure of the specification and the general knowledge in the field (see MPEP 2164.06).

Applicant notes that the Examiner believes that little prediction is possible in the field of biochemistry in the Office Action and that "detailed information regarding the structural and function requirements of the disclosed protein is lacking". Applicant respectfully disagrees. Despite the fact that proteins display an enormous array of functions, all are naturally composed of the same 20 amino acids, all governed by the same physico-chemical principles. These principles are represented quantitatively by the computational technique called PDA® (Protein Design Automation®) technology described in the specification, and embodied in US Patent Nos. 6,188,965; 6,269,312; 6,403,312; 6,708,120; 6,801,861; 6,804,611; 6,972,356; all of which have been either expressly incorporated by reference in the specification or are continuations of those cited therein.

The implication is that for the particular field of biochemistry that deals with protein structure engineering, predictive capacity does exist. In the article "Proteins from Scratch" (DeGrado, Science 278:80-81, 1997), Professor William F. DeGrado of the University of Pennsylvania School of Medicine, a world-renowned expert in protein structure, folding and design, comments on the PDA® computational platform designed by Dahiyat and Mayo in Science 278:82-87 (1997). This computational platform that was used to identify novel TNF-alpha variant proteins.

Dr. DeGrado states:

> "Not long ago, it seemed inconceivable that proteins could be designed from scratch. Because each protein sequence has an astronomical number of potential confirmations, it appears that only an experimentalist with the evolutionary life span of Mother Nature could design a sequence capable of folding into a single, well-defined three dimensional structure. But now on page 82 of this issue, Dahiyat and Mayo describe a new approach that makes de novo protein design as easy as running a computer."

Dr. DeGrado further states (col 1, paragraph 3):

> "Thus, the problem of de novo protein design reduced to two steps: selecting a desired tertiary structure and finding a sequence that would stabilize this fold. Dahiyat and Mayo have now mastered the second step with spectacular success. They have distilled the rules, insights and paradigms gleaned from two decades of experiments into a single computational algorithm...Thus the rules of ...computational methods for de novo design may now be sufficiently defined to allow the engineering of a variety of proteins".

Since the PDA® algorithm incorporates and utilizes physico-chemical properties of proteins well known and well established in the art, predictability is more than possible using the PDA® computational design technology used to identify the variant proteins of the present invention. In brief, the PDA® algorithm used in to identify protein variants of the present invention inputs structural coordinates of a specific wild type human TNF-α and analyzes potential variants based on the well established physico-chemical properties of the protein, amino acids and rotamers. Applicant is not "predicting a protein's structure and function from mere sequence data". Furthermore, PDA® technology takes into account the following concerns raised by the Examiner: "the positions within the protein's sequence where such amino acid changes can be made"; "positions in the sequence that are critical to the protein's structure/function relationship, e.g., such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites". The Examiner cites the Wells article for the proposition that "[T]hese regions can tolerate only relatively conservative substitutions or no substitutions". This article was published in 1990. The nature of the technology involving proteins has made significant advances in a decade, thus this statement isn't necessarily the case as of the priority date of Applicant's filing.

The use of the PDA® technology enables one to explore the possible diversity of variants at a particular positions, even the various sites and regions cited by the Examiner, and even non-conservative substitutions, because the technology is based on application of physico-chemical principles, which are general, and not on application of sequence similarity or conservation. In addition, Holmes (New Scientist, 11 October 1997) quotes the very same Dr. Wells where he states, "This [PDA® technology] will stand as a landmark piece of work".

The PDA® technology which is explained extensively in the specification and where the patents describing the technology are also incorporated by reference, provides more than adequate guidance "beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine without undue experimentation, the positions in the protein which are tolerant to change". In addition, Applicant has provided examples of combinations of amino acids in a sequence as compared to a wild type human TNF-alpha of SEQ ID NO: 2 in Figure 8b, for example.

The Examiner states that an ordinary artisan would ...recognize that an active or binding site must assume the proper three-dimensional configuration to be active..." The PDA®

technology addresses this issue, including rotameric configurations. The Examiner further states, "[T]here is not description of the activity contemplated by the changes by the Applicant". The application provides extensive disclosure about the mixed trimers generated in the present invention which uses at least one variant TNF-α monomer to generate a mixed trimer with a wild-type TNF-α monomer, where the variant sequence(s) inhibit or significantly decrease the activation of receptor signaling by a wild-type TNF-α protein. Figures 1A and 1B schematically show how the mixed trimers function. Furthermore, Applicant's use of a wild-type structure with the PDA® computational platform enables Applicant to recognize active or binding sites, and can deal with making appropriate substitutions; furthermore, the activity has been described extensively in the specification as well as Figure 1. The variants identified using the PDA® technology were made and tested to confirm that they variants met the specifically recited criteria in the claims. Applicant has shown that predicting which non-naturally occurring variants would retain the functions of the TNF-alpha protein is well within the realm of routine experimentation.

7e. Claim 28 is rejected under 35 USC § 112, first paragraph because the specification is not enabling for the activation of receptor signaling.

The claims now reflect that the receptor signaling is determined by a caspase activity assay. Thus, one skilled in the art can test for receptor signaling by an assay that is well known in the art.

Accordingly, Applicants respectfully submit that the specification enumerates a number of species to provide the proper basis for claims to the entire genus of variant TNF-α proteins and request withdrawal of the rejection under 35 USC § 112, first paragraph.

Rejection under 35 U.S.C. § 102

8. Claims 28-37, 46, 47 and 49 are rejected under 35 USC § 102(b) as being anticipated by Banner et al. (US 5,597,899) and as evidenced by Shin et al. (US 5,773,582).

An anticipation rejection requires that a single reference expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)). Additionally, the reference must enable and describe the claimed invention "sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." 31 USPQ2d at 1673. To be enabling, the reference must teach the skilled artisan how to make and use the full scope of the claimed invention without undue experimentation. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997).

The claims as amended overcome this rejection.

Banner et al. ("Banner")

Banner teaches the production of mutations at several different amino acid positions compared to wild type TNF-a, which has different binding affinity to p55-TNFR as compared to

p75-TNFR. Banner discloses human TNF-α muteins having higher binding affinity for human p75-TNF receptor than for human p55-TNF receptor. However, there is no disclosure in Banner regarding compositions comprising: a) isolated, mixed trimers comprising monomers with different amino acid sequences; or b) variants with the specifically recited amino acid changes at positions 21, 31, 32, 35, 66, 111, 112, 115, 140, 144, and 146.

Shin et al. ("Shin")

The Examiner states that the "evidentiary art of Shin...teaches that human TNF-α exist as a trimer with 3-fold axis of symmetry". While this observation is true, Shin does not suggest the use of mixed trimers (i.e., recited compositions of at least 2 TNF-α variants). Further, Shin does not disclose, suggest or teach the use of certain variants to sequences inhibit or significantly decrease the activation of receptor signaling by a wild-type TNF-α protein. Shin only discloses that TNF-α exists as a trimer. While it is not particularly clear in the Shin reference, it is believed that none of the Shin variants are the same as those identified in the instant case.

Shin also discloses that the muteins were tested for cytotoxicity in an in vitro anti-tumor activity assay that used direct cell-killing activity using a TNF sensitive cell line (see col. 4, line 66 – col. 5, line 39, col. 17, line 38 – col. 18, line 65) as well as for lethality (col. 18, line 66 – col. 20, line 16). Thus, the purpose of the mutants that Shin made was to kill TNF and for antitumor activity with a lower lethal toxicity. Applicant's variants are different than those of Shin and also are antagonistic in that they inhibit or significantly decrease the activation of receptor signaling by a wild-type TNF-α protein.

Banner as evidenced by Shin

The combination of both of Banner and Shin still does not teach the claimed invention. As stated above neither Banner nor Shin teach the novel variants as recited by Applicant in the claims. Neither reference, alone or in combination discloses the concept of variants that interact with wild type TNF-a to generate a mixed trimer that inhibits or significantly decreases the activation of receptor signaling by wt TNF-a. As can be seen from the above discussion, Banner does not disclose mixed trimers, or homo-trimers with the disclosed amino acid changes. Therefore, Banner does not explicitly teach or suggest each and every element of the claimed invention. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection under 102(b).

Rejection under 35 U.S.C. § 103

Claims 40-45 are rejected under 103(a) as being unpatentable over Banner in view of Wallach et al. (US 5,695,953) ("Wallach").

Claims 40-42 and 44-45 have been amended to depend either directly or indirectly from claim 38, which has been amended to be allowable (see Paragraph 11 in the Office Action).

Claim 43 is a method of making a mixed trimer with specifically recited variant positions. As stated previously with respect to Banner, there is no disclosure in Banner regarding compositions comprising: a) isolated, mixed trimers comprising monomers with different amino acid sequences; or b) variants with the specifically recited amino acid changes at positions in those claims. To combine Banner with Wallach, does not disclose teach or suggest Applicant's invention as Wallach does not teach mixed trimers, but only that use of a eukaryotic host enables proper folding and glycosylation. Further, there is no suggestion in Banner to glycosylate its muteins, and thus no suggestion to combine the references. Further Claim 43 has been amended to include specific variants not taught by either Banner or Wallach.

10. Claim 34 has been cancelled.

11. Applicant gratefully acknowledges the Examiner's indication that Claims 38, 39 and 47-49 would be allowable if written in independent form. Applicant has redrafted these claims to reflect this.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

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